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Brain Tumor Survivors

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## ABSTRACT

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Lisseth C. Calvio,   Master of Science, 2006

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*Introduction*

Malignant brain tumors survivors (BTS) can experience a number of symptoms including fatigue, emotional distress, and cognitive changes (e.g., memory problems) years following primary treatment. The magnitude of symptom burden in BTS and the relationship between these symptoms and cognitive limitations is unclear.

*Methods*

Factors associated with patient reported cognitive limitations (PRCL) were investigated in BTS (n=138) and a non-cancer comparison group (NCCG; n=155) using a web-based survey. Measures of demographics, medical factors, physical fatigue, depressive and anxiety symptoms, and factors impacting such symptoms (e.g., health behaviors and problem solving orientation) were measured to determine their association to PRCL.

*Results*

The BTS group was, on average, 4.8 years post diagnosis. Measures of fatigue *(t=6.08; p<0.001)*, depression *(t=6.42; p<0.001)* and anxiety *(t=3.70, p<0.001)* symptoms, negative problem solving orientation *(t= 2.69; p<0.001)* and cognitive limitations

$(t=8.24; p<0.001)$ were higher in the BTS group. The final model looking at symptom burden, health behavior, and problem solving indicated that depressive symptoms ($\beta=$ 0.18; p=0.03) and negative problem solving ($\beta= 0.45$; p<0.001) accounted for 46% of the variance in cognitive limitations in both groups.

*Conclusions*

BTS experienced higher levels of symptom burden, yet cognitive limitations were independently related to depressive symptoms and negative problem solving orientation in both groups. These findings suggest that interventions directed at both depressive symptoms and problem solving style may improve cognitive limitations in BTS. The combination of efforts should be evaluated and if necessary specifically targeted for intervention.

# PATIENT REPORTED COGNITIVE LIMITATIONS IN BRAIN TUMOR

## SURVIVORS

by

Lisseth Carmen Calvio

Thesis submitted to the Faculty of the

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*Introduction*

The standard treatment for primary malignant brain tumors includes surgical resection, 4-6 weeks of conventional fractioned radiotherapy, with or without adjuvant chemotherapy [1]. Radiation has been associated with cognitive limitations through several possible mechanisms. Radiation may destroy oligodendrocytes leading to demyelination and loss of white matter in the brain [2]. Radiation may also impact endocrine pathways and function [3]. These changes can directly contribute several cognitive limitations commonly experienced by brain tumor survivors (BTS) [4]. Nonspecific neurological complications have also been associated with chemotherapy, and include central neurotoxicity, acute encephalopathy, and microvascular changes which can be manifested as decrements in psychomotor processing, nonverbal memory, attention and other cognitive limitations [5, 6]. However, the nature of these changes and its effects on cognitive functioning in the everyday world are unclear. These cognitive changes can be influenced by several disease or treatment related factors, such as tumor type, location, and of chemotherapy agent used and dose and location of brain radiation [2, 3, 7, 8].

Seizures are also often experienced by BTS either as a presenting symptom (15% to 20%) or as a symptom that develops over time (10 to 30%) [9]. Seizures themselves have been associated with neuronal injury and cell death as well as increased intracranial pressure and cerebral herniation [9]. The medications used to treat seizures may also have a negative impact on cognitive function. Common side effects can include sedation, language dysfunction, psychomotor slowing, depression, anxiety, behavioral changes, and fatigue [9]. .

In certain non-cancer populations with persistent fatigue, subtle changes in information processing, attention, and memory can occur [10]. For cancer survivors in general, fatigue is one of the most common side effects of the cancer experience [10]. Depressive symptoms and cognitive limitations, such as problems with memory and attention, are often concurrently experienced in BTS [11, 12]. This triad of symptom burden (depressive symptoms, fatigue, and cognitive impairment) appears to be related in cancer survivors; however, the nature of this relationship is currently unclear [10]. Anxiety and emotional distress are also experienced by some brain tumor survivors [13]. Higher levels of anxiety can have a negative effect on cognitive functioning. When acute anxiety symptoms (i.e., panic attacks) are induced in healthy men, deficits in attention, visuospatial memory, and mental flexibility are reported [14]. Although cancer survivors may not experience anxiety in an acute form, anxiety may be significant [13]. These data suggest that the anxiety experienced by brain tumor survivors may also negatively impact cognitive processes and merits further investigation.

One approach that can potentially impact the symptom burden of cancer survivors is a set of skills related to problem-solving [15]. Individuals who cope poorly with various stressful events tend to demonstrate deficits in problem-solving skills [16]. As BTS cope with such stressors as cognitive challenges, problem solving abilities may help to attenuate these problems on daily function. In fact, Edvardsson and Ahlstrom [11] found that for low-grade brain tumor survivors, the coping strategy of actively "searching for a solution" was significantly used to cope with memory and communication difficulties. Effective problem solving skills can help survivors generate possibilities for alternative solutions to several challenges [16]. Certain health behaviors

have the potential to impact cognitive function as well [17, 18]. Brain tumor survivors commonly experience sleep disturbances [19]. Although the effects of sleep disturbances on cognitive function have not been investigated with BTS, studies using healthy populations and those with obstructive sleep apnea have indicated that sleep loss, sleep reduction, and fragmented sleep are associated with decrements in executive functioning [17]. Exercise can also serve as a buffer or may create changes in the brain that may decrease cognitive limitations. A meta-analysis [18] found improvements in executive function, visual-spatial tasks, and processing speed in community-dwelling healthy older adults, ranging from young-old, 55 years old, to old-old, 71+ years old.

Factors including the illness itself, cancer therapy, fatigue, and emotional distress can bi-directionally affect each other as well as potentially influence cognitive limitations. Health behaviors and problem solving may mitigate the relationship between illness variables and symptom burden, by decreasing the burden of cognitive limitations. An individual with an aggressive malignant brain tumor, followed by significantly invasive cancer therapy, high levels of physical fatigue and distress, may experience high levels of self-reported cognitive limitations. It is further assumed that having a healthy life style along with a positive problem solving style may help to minimize the impact of triggering factors on cognitive function (figure 1).

The purpose of this cross-sectional, internet-based, pilot study was to investigate the independent contributions of emotional factors (depression, anxiety), fatigue, health behaviors, and problem solving on cognitive limitations, while accounting for demographic and brain tumor related variables. It was of particular interest to determine

whether this relationship differed in BTS relative to a non-cancer comparison group (NCCG).

## *Methods*

The data used in this study were extracted from a larger study that investigated factors that impact work productivity in brain and breast cancer survivors. A web-based questionnaire was placed online on a secure site using the Test Pilot program [20]. The online assessment required an average of 1 hour and 45 minutes for respondents to complete. An e-copy of the questionnaire may be obtained by contacting the researchers. The study protocol received approval from both the Uniformed Service University of the Health Sciences and the American University Institutional Review Boards. Completion of an online consent form was required prior to accessing the questionnaire. All information was kept confidential; the participant's name and identifying information were stored separately from the rest of the data. Upon completion of the questionnaire, participants had an option of submitting a name and address to receive a "LIVESTRONG" wristband and a check for compensation ($15.00 US) for their time. The questionnaire responses were downloaded weekly and entered into an Excel spreadsheet and imported to SPSS version 12.0. All data analyses were conducted with SPSS version 12.0.

### *Inclusion Criteria*

Participants were between 20-70 years old and of various ethnicities. A minimum of a self-reported 7th grade English reading proficiency level was required for participation. As part of the inclusion criteria for the larger study, BTS were working full time or part-time for at least one year prior to diagnosis, and were working during the

time they completed the survey.  Participants in the NCCG were required to be employed

for a minimum of one year at the time of the study and were free of additional (e.g., non-

cancer) chronic illnesses.

*Recruitment*

Adult BTS and NCCG were recruited from brain tumor organization websites,

including the Brain Tumor Society (www.tbts.org), the National Brain Tumor Foundation

(www.nbtf.org), and the American Brain Tumor Association (www.abta.org), through

brain tumor support groups in Washington, D.C. and Baltimore, MD and distribution of

flyers at brain tumor fundraisers, such as the Race for Hope.  Newspaper advertisements

were also placed in the *Washington Post* and *NIH Record* to recruit both cancer survivors

and NCCG.

*Procedures*

The first step involved completing a seven question on-line screen assessing for

the inclusion criteria (http://cim01.usuhs.mil/mps/jhansen/Inclusion.tp4?manage).

Individuals who met the inclusion criteria were contacted via e-mail and were given a

username and password to the website containing the survey

(http://cim01.usuhs.mil/mps/jhansen/CancerSurvey.tp4).  Individuals who did not meet

the criteria were contacted via e-mail with an explanation as to why they were excluded.

Participants were able to contact researchers via telephone or e-mail if any questions or

comments arose.

*Measures*

The measures included in this analysis assessed medical status, mood, anxiety, fatigue, patient reported cognitive limitations (PRCL), and health behaviors. The measures are described below.

*Medical Status.* Participants were asked to complete a series of forced choice questions regarding medical history. These questions included type of tumor, stage of tumor, treatment received (surgery, radiation, and/or chemotherapy), dose of radiation, months on chemotherapy, date of diagnosis, medications, co-morbid health conditions, and availability of health insurance.

*Hospital Anxiety and Depression Scale (HADS).* The HADS is a self-assessment scale for measuring depression and anxiety in a general medical population [21]. The HADS consists of 14 items consisting of two subscales, one measuring Anxiety (A-scale) and one measuring Depression (D-scale), which are scored separately. The HADS was included in the present study to detect elevations in symptoms of depression and anxiety.

*Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SI).* The MFSI-SF is a 30-item self-report measure of fatigue encompassing five symptom domains: general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor [22]. In an effort to control for redundancy of measurement (e.g., components of emotional fatigue being captured by depression measure), physical fatigue was the dimension of interest and was the only scale used to represent fatigue in the analysis.

*Behavioral Risk Factor Surveillance Survey.* Questions from the Behavioral Risk Factor Surveillance Survey [23] measure were included to provide an assessment of the frequency of aerobic, strengthening, and stretching exercises (rarely, 1 or 2 times per

week, at least 3 times per week). These questions also assessed smoking status (never smoked, used to smoke, still smoke), adequate nutrition (yes/no), and whether participants felt that they generally received sufficient sleep (yes/no).

*Social Problem Solving Inventory-Revised (SPSI-R).* The Social Problem Solving Inventory (SPSI-R) measures both adaptive problem-solving dimensions and non functional dimensions (e.g., negative problem orientation, impulsivity/carelessness style, and avoidance style) [24, 25]. This study used the negative problem solving orientation subscale as a measure of difficulties with problem solving.

*Cognitive Symptom Checklist-select items (CSC).* While the gold standard for assessment of cognitive function is objective neuropsychological testing [26, 27], it was reasoned that both long term BTS and NCCG would be able to provide a dichotomous response as to whether they experienced functional problems in everyday life related to memory, organization, and attention. In addition, neuropsychological batteries assess performance on certain tasks and it is unclear whether these results generalize to the manifestation of these deficits in the survivor's daily life or subjective experience [28]. We focused on PRCL using a questionnaire with several examples of common forms of cognitive limitations (e.g., constantly forgetting where you left your keys.) Furthermore, a self-report measure allowed for ease of distribution and administration via the Internet.

The measure of PRCL was modified from the Cognitive Symptoms Checklist (CSC), which was developed for use as a patient checklist to assist in orienting providers to patient reported cognitive problems [29]. The CSC was converted to a self-report index of disruption of tasks that require specific cognitive functions (dichotomous discrimination; i.e., problem/not a problem). The CSC has been used to assess PRCL

difficulties in individuals with neurological insults, such as head injuries and brain tumors. These problems include attention/concentration, memory, visual processes, and executive function. The items were reduced from 100 to 83 items following a varimax factor analysis that revealed a three-factor solution representing working memory *(Cronbach's α= 0.93)*, executive functioning *(Cronbach's α= 0.91)*, and attention *(Cronbach's α= 0.86)*. The CSC was further reduced to 59 items by selecting only items with a factor loading of 0.4 or higher on one of these three factors. This modified version of the CSC was used as a patient reported index of cognitive difficulties encountered by participants in daily life. The average of this score was the dependent variable for the regression model. Detailed information regarding the reduction of items is available.

*Analysis*

Chi square and t-tests were performed to assess for differences in participant characteristics, health behaviors, triggering factors (anxiety, depressive symptoms, fatigue), and self-reported cognitive limitations. Correlations were conducted to determine relationships among the variables of interest. Missing data were substituted with either the mean for continuous variables and median for categorical variables [30]. Items that had more than 5% missing data were excluded from the analyses.

In order to reduce the number of independent variables for the final multivariable regression model, bivariate correlations and regression analyses were employed [31]. Symptom burden and health behavior variables that were significantly correlated with cognitive limitations ($p<0.05$) were included in the final regression model. Demographic and medical variables were analyzed for their relationship to cognitive limitations ($p<0.10$) using linear regression. These data reduction techniques resulted in a model of

fifteen variables entered in six steps.  The model included cancer status (cancer/non-cancer) and the interactions of cancer status with each of the variables.

<div align="center">*Results*</div>

*Participant Characteristics*

Table 1 lists participant characteristics for the BTS and NCCG.  The study consisted of 138 malignant BTS and 155 NCCG.  The largest percentage of survivors was between the ages of 40 to 49 (37%), followed by 50 to 59 (26%), and 30 to 39 (22%).  The BTS were on average 4.80 (SD=3.90) years post-diagnosis, ranging from 1 to 17 years post-diagnosis.  The mean age was 42.87 years (SD = 10.02) for BTS, and 39.61 years (SD=11.20) for NCCG.  Gender *($\chi^2$ (1) = 14.33, p<0.001)*, education *($\chi^2$ (5) = 11.10, p=0.05)*, and marital status *($\chi^2$ (3) = 12.73, p<0.001)* differed significantly across both groups.  The BTS group was 57% female, while the NCCG was 78% female.  The sample was well educated, as 70% of the BTS group and 82% of the NCCG had an associates degree or higher.  Seventy-four percent of the BTS group, compared to 55% of the NCCG was married at the time of the study.  93% of the BTS and 89% of the NCCG are self-identified as Caucasian.

Table 2 describes medical status of the BTS.  The three most common brain tumor types were glioblastomas (23%), astrocytomas (32%), and oligodendrogliomas (36%).  All cancer stages were represented in the BTS sample with stage II (42%) being the highest.  BTS reported multiple areas for tumor location; the most common areas were the right hemisphere (48%) and frontal lobe (22%).  Surgery-biopsy (88%), radiotherapy (72%), and chemotherapy (65%) were reported at high rates.  Half of the BTS sample reported undergoing a combination of surgery, radiation, and chemotherapy.

For those receiving radiotherapy, the majority (69%) was unsure as to the amount received.  Of those receiving chemotherapy, the majority (66%) received chemotherapy from 6 to 17 months.  This sample was reflective of the types of tumors and treatment of those with malignant brain tumors [32].

Current medication use was assessed.  Antiepileptic medications were reported by 63% of the BTS and 1% of the non-cancer comparison group $(\chi^2 (1) = 131.64, p<0.001)$. Significantly fewer BTS participants reported taking no medications than non-cancer comparisons $(\chi^2 (1) = 9.99, p<0.01)$.  These data indicate that BTS report taking more medications in general and were using antiepileptic medications. Current health behaviors between the BTS and the NCCG were also assessed.  BTS reported significantly lower levels of aerobic exercise $(\chi^2 (2) = 12.17, p<0.01)$, strengthening exercise $(\chi^2 (2) = 8.35, p=0.02)$, and poorer sleep $(\chi^2 (1) = 15.27, p<0.001)$. Also, the BTS sample was more likely to be married and male in comparison to the NCCG. The association of these factors with cognitive limitations was accounted for in the analyses.

T-tests (Table 3) were run to compare differences in physical fatigue, depressive symptoms, anxiety symptoms, negative problem solving orientation, and PRCL between the BTS and NCCG.  BTS were significantly more likely to endorse a negative problem solving orientation $(t= 2.69; p<0.001)$ and were more likely to report higher levels of physical fatigue $(t=6.08; p<0.001)$, anxiety $(t=3.70, p<0.001)$, depressive symptoms $(t=6.42; p<0.001)$, and cognitive limitations $(t=8.24; p<0.001)$.

*Variable reduction*

A two-step variable reduction technique was then administered.  First, a linear regression was run with all of the variables related to medical and demographic factors as

independent variables to determine their contribution to cognitive limitations. Mood medication was the only significant factor and subsequently, the only medical variable used in the main regression. The second step of the reduction technique involved looking at correlations between enabling factors and cognitive limitations. The variables that were significantly correlated with PRCL are reported in table 4. Cancer status (r=0.44, p<0.001), anxiety (r=0.44; p<0.001), depression related symptoms (r=0.51, p<0.001), physical fatigue (r=0.40, p<0.001), aerobic exercise (r=-0.13, p<0.05), and negative problem solving orientation (r=0.51, p<0.01) were significantly correlated with cognitive limitations.

*Factors Associated with Cognitive Limitations*

The regression model (Table 5) accounted for 46% *(R$^2$ = 0.46; p<0.53)* of the variance in cognitive limitations. Within the model, depressive symptoms *(ß = 0.18; p=0.03)* and negative problem solving orientation *(ß = 0.45; p<0.001)* were significantly and independently associated with PRCL. None of the interactions were significant, indicating that cancer status did not contribute to cognitive limitations.

Discussion

These findings indicate higher levels of distress and physical fatigue, poorer sleep, a more negative approach to solving problems, and a higher level of self-reported cognitive limitations in survivors of brain tumors almost five years post diagnosis than individuals without cancer. This burden was observed in working adults. Despite these differences, depressive symptoms and negative problem solving orientation were associated with cognitive limitations in both groups. These findings indicate that

although the symptom burden is higher in brain tumor survivors, changes in cognitive limitations are associated with the same factors as those without cancer and its treatment sequelae. It is important to highlight that these findings accounted for a number of relevant demographic and medical factors that have been proposed in past research to be related to cognitive limitations.

The level of depressive symptoms was related to cognitive limitations in both groups. It is interesting to note that the percentage of BTS who reported taking mood medication (22%) did not significantly differ from the NCCG (18%). It is possible that antidepressants or other medications may improve some aspects of cognitive limitations even at the sub-syndromal levels of depression experienced by both groups. There are also non-pharmacological approaches, such as exercise [33, 34] and cognitive behavioral interventions [35, 36] that also may be useful in reducing depression and its association to cognitive limitations. These approaches need to be systematically investigated in brain tumor survivors.

Problem solving can serve as a moderator between negative life stressors and depressive mood [37]. As expected, moderately depressed individuals experience problems in ability to cope in response to daily stressors [38, 39, 16]. In the present results, negative problem solving orientation and depressive symptoms were related. However, it is important to emphasize that both factors were independently related to cognitive limitations although the direction of this relationship needs to be clarified.

For many, depressive symptoms can include a decrease in memory and attention. The HAD-depression subscale recorded areas including "loss of interest" and "diminished pleasure" [21], and not neuro-vegetative symptoms. The results suggest that

these two dimensions of depression are independently associated with cognitive

limitations and targeting these areas may serve to improve subjective cognitive function.

This is an area requiring further investigation. Effortful coping with challenges in

cognitive function appear to be very important.

*Study Limitations*

There are limitations related to the cross-sectional nature of this study.  For

instance, it is unclear whether the cognitive limitations reported were related to cancer

diagnosis and/or treatment or if the limitations were present prior to the cancer diagnosis.

It is also important to emphasize the preliminary nature of this investigation. Participants

were primarily recruited from cancer survivor websites and the study was conducted via

the Internet.  This may have created a selection bias for individuals who had knowledge

of the Internet, these specific websites, as well as access to the Internet.  The sample

consisted of individuals that were mostly Caucasian, married, highly educated with jobs

and health insurance. The work history and health insurance was a requirement of the

overall study. It is important not to over generalize from this sample. Given the sample, it

is important to point out that the two variables associated with cognitive limitations were

factors that can impact emotional and motivational elements of adapting to an illness.

Future studies with diverse groups of those with brain tumors and various comparison

groups need to be conducted.

Longitudinal research that measures depressive symptoms, problem solving, and

cognitive function should also be conducted to determine the direction and specificity of

the relationships. All measures were self-reported, including the information used to

ascertain groups. Recall bias could have been operating.  However, while not optimal

there are data on breast cancer survivors indicating that at three years post diagnosis these survivors were able to accurately recall medical information (i.e., treatment exposure [40]. Also, when compared to collateral data collected from nursing staff regarding patient symptoms and functioning (e.g., cognitive and emotional functioning), cancer patients were found to accurately report symptoms [41].

Conventional neuropsychological evaluation is considered the "gold standard" for assessing cognitive function [26]. The self-reported functional problems observed in the present study related to functional activities that involve working memory, executive function, and attention did appear to capture many challenges reported in the literature experienced by those with brain tumors [4]. The relationship between depressive symptoms, problem solving and cognitive function requires confirmation in BTS using both neuropsychological testing and other self-reported measures. Greater understanding of these relationships and the unique contribution of different measurement technologies can lead to more accurate measurement of these cognitive limitations reported by many cancer survivors. Poppelreuter et al. [42] indicated that neuropsychological and subjective measures may capture different aspects of cognitive function. (e.g., population norms vs. cognitive limitations on a daily basis) [42]. Our measure of cognitive limitations was significantly associated with HADS depression and anxiety scores, which is consistent with the literature using the HADS with standard neuropsychological testing [43]. This pattern of results suggests that the measure of cognitive limitations used behaves in ways similar to structured testing. However, future research needs to validate the self-report measure against neuropsychological testing and some measure of actual daily cognitive functioning.

This preliminary investigation indicates that despite differences on measures reflecting distress, health behaviors, and problem solving; depressive symptoms and a more negative problem solving orientation similarly affect cognitive limitations in brain tumor survivors, on average five years post-diagnosis, and individuals without cancer. While actual brain function may differ (e.g. slower brain processing) [4], addressing these factors in both groups can potentially enhance cognitive function. Efforts to improve daily challenges in cognitive function related to everyday tasks at work and home represent a potentially useful goal in brain tumor survivors.

*Table 1.*
Paticipant Characteristics

| | Brain Tumor (n= 138) | | Non-Cancer Comparison Group (n=155) | |
|---|---|---|---|---|
| | N | % | N | % |
| Age | | | | |
| 20-29 | 17 | 12 | 36 | 23 |
| 30-39 | 30 | 22 | 47 | 30 |
| 40-49 | 51 | 37 | 37 | 24 |
| 50-59 | 36 | 26 | 30 | 19 |
| 60-70 | 4 | 3 | 5 | 3 |
| Gender*** £ | | | | |
| Female | 79 | 57 | 120 | 78 |
| Male | 59 | 43 | 34 | 22 |
| Education* | | | | |
| Less than HS/HS/GED | 14 | 10 | 8 | 5 |
| Some college | 28 | 20 | 19 | 12 |
| A.A. or Bachelors | 43 | 31 | 41 | 26 |
| Some graduate school | 16 | 12 | 23 | 15 |
| Graduate degree | 37 | 27 | 64 | 41 |
| Marital Status*** | | | | |
| Single | 16 | 12 | 38 | 25 |
| Cohabitating | 5 | 4 | 12 | 8 |
| Divorced/separated/widowed | 15 | 11 | 19 | 12 |
| Married | 102 | 74 | 86 | 55 |
| Race | | | | |
| Caucasian | 128 | 93 | 138 | 89 |
| Non-Caucasian | 10 | 7 | 17 | 11 |

*p<0.05; **p<0.01; ***p<0.001
£= 1 participant in NCCG did not indicate gender. This missing data point was not substituted.

*Table 2.*
Brain Tumor Survivor: Tumor Type and Treatment

| | n | % | | n | % |
|---|---|---|---|---|---|
| Tumor type (n=138) | | | Radiation dose (n=97) | | |
| Glioblastoma | 32 | 23 | < 40 Gy | 4 | 4 |
| Astrocytoma | 44 | 32 | 46-50 Gy | 1 | 1 |
| Oligodendroglioma | 49 | 36 | 51-55 Gy | 6 | 6 |
| Malignant glioma | 5 | 4 | 56-60 Gy | 8 | 8 |
| Ependymoma | 8 | 6 | > 60 Gy | 11 | 11 |
| Tumor grade (n=132) | | | Not Sure | 67 | 69 |
| I | 12 | 9 | Months on chemotherapy (n=88) | | |
| II | 55 | 42 | 1-5 months | 16 | 18 |
| III | 35 | 27 | 6-11 months | 27 | 31 |
| IV | 30 | 23 | 12-17 months | 31 | 35 |
| Tumor location (n=138)¥ | | | 18-23 months | 4 | 5 |
| Right hemisphere | 66 | 48 | 24-29 months | 10 | 11 |
| Left hemisphere | 94 | 68 | | | |
| Bilateral | 4 | 3 | | | |
| Front | 30 | 22 | | | |
| Middle | 15 | 11 | | | |
| Back | 19 | 14 | | | |
| Treatment type (n=138)¥ | | | | | |
| Chemotherapy | 90 | 65 | | | |
| Radiation | 100 | 72 | | | |
| Chemotherapy/radiation | 73 | 53 | | | |
| Surgery | 122 | 88 | | | |
| Chemotherapy/radiation/surgery | 69 | 50 | | | |
| Other treatment | 15 | 11 | | | |

¥= categories allowing for more than one answer

*Table 3.*
Measure of Symptom Burden

| | Brain Tumor (n=138) | | Non-Cancer Comparison (n=155) | |
|---|---|---|---|---|
| | M | SD | M | SD |
| MFSI Physical Fatigue Subscale*** | 5.47 | 5.36 | 2.39 | 2.73 |
| HADS Depression*** | 6.14 | 4.43 | 3.21 | 3.19 |
| HADS Anxiety*** | 7.78 | 4.15 | 6.10 | 3.52 |
| Cognitive Limitations*** | 23.69 | 13.76 | 12.00 | 9.96 |

*p<0.05; **p<0.01; ***p<0.001

*Table 4.*
DemogrSignificant Correlations with Cognitive Limitations for BTS and NCCG (n=293)

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| 1 CSC | --- | -0.44*** | -0.13* | 0.51*** | 0.40*** | 0.44*** | 0.51*** |
| 2 Cancer Status | -0.44*** | --- | 0.14* | -0.16** | -0.35*** | -0.21*** | -0.36*** |
| 3 Aerobic Activity | -0.13* | 0.14* | --- | -0.14* | -0.19** | -0.14* | -0.29*** |
| 4 Negative Problem Solving | 0.51*** | -0.16** | -0.14* | --- | 0.29*** | 0.58*** | 0.48*** |
| 5 Fatigue | 0.40*** | -0.35*** | -0.19** | 0.29*** | --- | 0.45*** | 0.52*** |
| 6 HADS Anxiety | 0.44*** | -0.21*** | -0.14* | 0.58*** | 0.45*** | --- | 0.64*** |
| 7 HADS Depression | 0.51*** | -0.36*** | -0.29*** | 0.48*** | 0.52*** | 0.64*** | --- |

*Table 5.*
Factors Related to Patient-Reported Cognitive Limitations  (n=293)

| Step | R | Cumulative $R^2$ | $\Delta R^2$ | $\Delta F$ | *P* |
|---|---|---|---|---|---|
| 1. Cancer Status*** | 0.44 | 0.19 | 0.19 | 69.48 | 0.00 |
| 2. Emotional Distress*** | 0.60 | 0.36 | 0.17 | 38.40 | 0.00 |
| 3. Medication | 0.61 | 0.37 | 0.01 | 3.33 | 0.07 |
| 4. Fatigue | 0.61 | 0.38 | 0.01 | 2.17 | 0.14 |
| 5. Protective Factors*** | 0.67 | 0.45 | 0.08 | 19.68 | 0.00 |
| 6.  Interactions | 0.68 | 0.46 | 0.01 | 0.85 | 0.53 |

| Variables | Beta | Partial | *t* | *p* |
|---|---|---|---|---|
| 1.  Cancer Status | | | | |
|    Cancer Status | -0.26 | -0.08 | -1.38 | 0.17 |
| 2.  Emotional Distress | | | | |
|    Anxiety Symptoms | -0.13 | -0.05 | -0.89 | 0.37 |
|    Depressive Symptoms* | 0.18 | 0.13 | 2.21 | 0.03 |
| 3.  Medication | | | | |
|    Mood medication | 0.17 | 0.10 | 1.60 | 0.11 |
| 4.  Fatigue | | | | |
|    Physical fatigue | -0.05 | -0.03 | -0.46 | 0.65 |
| 5.  Protective Factors | | | | |
|    Aerobic Exercise | 0.07 | 0.04 | 0.67 | 0.51 |
|    Negative Problem Solving*** | 0.45 | 0.22 | 3.84 | 0.00 |
| 6.  Interactions | | | | |
|    Depressive Symptoms x Cancer Status | -0.06 | -0.04 | -0.58 | 0.56 |
|    Anxiety Symptoms x Cancer Status | 0.18 | 0.07 | 1.15 | 0.25 |
|    Fatigue x Cancer Status | 0.16 | 0.10 | 1.59 | 0.11 |
|    Negative Problem Solving x Cancer Status | -0.17 | -0.06 | -1.02 | 0.31 |
|    Aerobic Exercise x Cancer Status | -0.04 | -0.01 | -0.24 | 0.81 |
|    Mood Medication x Cancer Status | -0.07 | -0.04 | -0.62 | 0.53 |

*p<0.05; **p<0.01; ***p<0.001

***Figure 1.*** **Cognitive Limitations and Brain Tumor Survivors**

**Demographics**
•Gender
•Ethnicity
•Age
•Marital Status
•Education

**Triggering Factors**

**Distress**
•Depressive Symptoms
•Anxiety Symptoms
•General Distress

**Medical Factors**
•Type of Tumor
•Stage Diagnosed
•Cancer Tx
•Medications
•Seizures

**Fatigue**
•Physical Fatigue
•Mental Fatigue
•Emotional Fatigue

**Enabling Factors**

**Health Behaviors**
•Physical Activity
•Sleep
•Smoking Behaviors
•Diet
•Social Support

**Problem Solving** Orientation
•Positive Problem Solving
•Negative Problem Solving

**Cognitive Limitations**
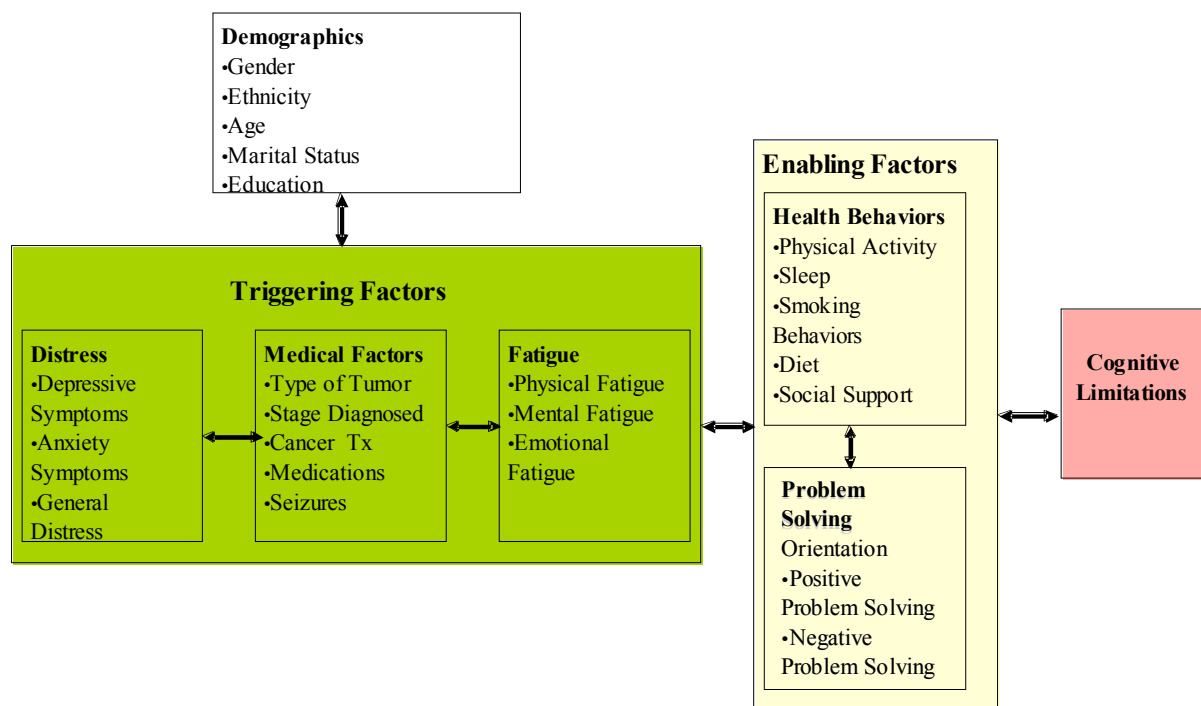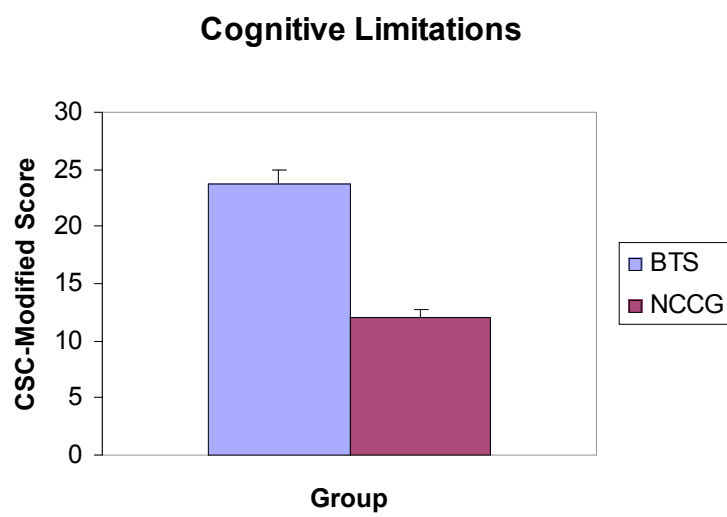
*Figure 2.* **Cognitive Limitation Score**



**Cognitive Limitations**

**Appendix 1**

Abbreviated Cognitive Symptoms Checklist

**Memory:**

**I have difficulty:**
1.  doing math in your head
2.  answering questions quickly (for example, when someone asks a question or when you write answers down
3.  understanding what you read without rereading it
4.  understanding what you hear the first time you hear it
5.  seeing mistakes that you make as they occur
6.  seeing mistakes after you have completed the task
7.  shifting my attention among two or more things (for example, listening to someone talk while rereading my e-mail)
8.  shifting from one task or activity to another (for example, switching from working on the computer to taking a phone call)
9.  completing all steps of a task or activity
10. following step-by-step instructions
11. following written instructions
12. writing to other people in an organized manner (so it makes sense to them)
13. organizing information to be remembered
14. following or retracing steps to solve a problem (for example, to locate a lost item)
15. remembering to perform daily routines (for example, check e-mail, respond to e-mail, check phone messages)
16. remembering things someone has asked me to do
17. remembering the content of telephone conversations
18. remembering the content of conversations and/or meetings
19. remembering a word you wish to say
20. remembering your train of thought as you are speaking
21. remembering the name of a familiar object or person
22. remembering information that's "on the tip of my tongue"
23. remembering what you intended to write
24. focusing on a task when there is too much detail or clutter (for example, reading a newspaper page with small print)

**Executive Function:**

**I have difficulty:**
1.  seeing and correcting mistakes on your own
2.  seeing and correcting mistakes pointed out to you by others
3.  trying new ideas or actions
4.  planning a speech
5.  planning what to discuss when you meet someone (for example, your doctor, attorney, insurance agent)
6.  following directions to a specific place

7. putting steps in order such that the most important steps are done first
8. setting up a routine or system to approach tasks
9. understanding what a problem is when it occurs and clearly stating what the problem is
10. knowing where to look for information to solve a problem
11. using new information to re-evaluate what you know
12. choosing a solution to a problem from several possible sources
13. acting on a decision that you made
14. putting together the materials needed for a task
15. understanding a system (for example, how the members of a team work together)
16. understanding graphs or flowcharts
17. understanding how a task fits into a plan or system
18. understanding systems and models (for example, politics at work)
19. figuring out how a decision was reached
20. following the flow of events (for example, in a meeting)
21. considering all aspects of what you hear or see instead of focusing on only one part
22. remembering to schedule appointments
23. remembering to keep appointments once they are scheduled

**Attention:**

**I have difficulty:**
1. focusing on a task when there is too much detail or clutter (for example, reading a newspaper page with small print)
2. making decisions
3. staying with a task until completion
4. starting a task or activity on your own (without having others remind or motivate you
5. remembering where your car is parked
6. focusing on a task when there is a sudden movement around you
7. focusing on a task when there is a lot of movement happening around you
8. focusing on a task when there is a sudden loud noise (for example, siren, horn, car alarm)
9. focusing on a task when more than one person is speaking at a time
10. focusing on a task when a radio or TV is playing in the background
11. focusing on a task when you feel hot or cold
12. focusing on a task when you are in a large area (for example, in a lobby of a building or in a large gathering in an auditorium)
13. staying focused in places where there are many sights and sounds

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